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CASE REPORT

Vagus nerve stimulation for refractory epilepsy

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CASE REPORTS

Case 1

This 36 year-old, right-handed female nurse presented at the Ghent University Hospital Epilepsy Clinic in 1997. She was one of healthy twins who had had a normal delivery after an uneventful pregnancy. At the age of 3 years she was diagnosed with aseptic meningitis and made a full recovery. At the age of 23 years she had a first episode of sudden loss of contact, nonsense speech and shaking of both hands. She was first treated with carbamazepine. This was combined with valproate after 2 years. After an unsuccessful trial with fenytoin, she was treated with a combination of vigabatrin 2000 mg/day and carbamazepine 1400 mg/day. At the age of 33 years when she was first evaluated at our centre she had at least two habitual seizures per month. She had been on disability for over 2 years. The seizures consistently began with a feeling of discomfort in her head. This was followed by loss of contact, nonsense speech, cyanosis of the lips and shaking of the upper extremities. The whole episode would last up to 45 seconds. Afterwards she experienced a period of confusion of up to 15 minutes. There was occasional secondary generalization. Family history was negative for neurological diseases. Routine EEG showed diffuse theta waves and focal sharp transients in the left temporal electrodes. Prolonged video-EEG monitoring showed an interictal spike focus with phase reversal over the anterior temporal region (F7). Seven habitual seizures were recorded. The semiology was suggestive of a temporal lobe seizure origin; ictal EEG showed left frontotemporal recruitment of rhythmic theta activity. Optimum MRI showed bilateral hippocampal damage. Interictal FDG-PET showed bilateral extended areas of hypometabolism in the temporal lobes. Neuropsychological assessment was suggestive of bilateral medial temporal lobe dysfunction. On the basis of the pre-surgical assessment the hypothesis was that the patient had complex partial seizures originating in the left (medial) temporal lobe. She subsequently underwent an intracarotid amytal procedure which demonstrated a left-sided hemispheric language dominance and a severe memory deficit on the right side. It was felt that the patient was not a candidate for further evaluation since the results of the Wada-test excluded any resective procedure involving medial temporal lobe structures on the left side. She was offered VNS instead. The generator was implanted in September 1998. The antiepileptic drug regimen was unchanged. The surgical procedure and post-surgical follow-up were uneventful. The generator was activated 2 weeks after the implantation; subsequently the stimulation output was increased by 0.25 mA increments. During the ramping up period, the patient complained of intermittent mild hoarseness. Three months following the implantation when the output current reached 1.25 mA she had a single generalized tonic–clonic seizure after 1 month of seizure freedom. The output current was further increased to 1.5 mA with standard stimulation parameters. The patient's husband used the magnet for delivering additional stimulation trains which allowed to abort generalized seizures. During regular follow-up with intervals of 6 weeks, the average frequency of habitual seizures decreased from at least two per month to less than two per 6 months. She is again gainfully employed.

Case 2

This 26 year-old right-handed female with a history of perinatal asphyxia developed generalized tonic–

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clonic seizures at the age of 1 year. At the age of 3 years she had daily atonic seizures and frequent convulsions. She developed psychomotor retardation and was admitted into a special care facility for epileptic children for a 2-year period. There she was treated with all available antiepileptic drugs. Despite wearing a helmet during the daytime she suffered frequent head trauma. At the age of 22 years, she was treated with carbamazepine 1800 mg/day and clobazam 10 mg/day. Video-EEG monitoring documented daily atonic episodes, complex partial seizures with frontal semiology, generalized convulsions and myoclonic jerks. The interictal EEG showed a slow background activity with frequent slow spike wave and polyspike complexes. During atonic and partial seizures, the EEG showed an electrodecrement and muscle artefacts. Neuropsychological assessment showed an estimated IQ score of 45. Optimum MRI showed strictly no structural abnormalities. The clinical diagnosis of LGS was made. The patient underwent an anterior 2/3 callosotomy in February 1993. After the surgical procedure she had no focal neurological deficit. She subsequently became free of generalized convulsions and had fewer atonic seizures. This allowed her to stop wearing her helmet. Two years after the callosotomy, she started having convulsive seizures again. She was subsequently treated with lamotrigine, vigabatrin, felbamate and clonazepam in various combinations. In 1998 she had daily atonic seizures and frequent states of loss of contact that lasted many hours. The patient was again admitted to the video-EEG monitoring unit and habitual seizures were recorded. Based on the study of the ictal semiology of the different seizure types and ictal EEG traces, the diagnosis of LGs was reconfirmed. In March 1999, an NCP^{TM} device was implanted. Within a few weeks during which the output current was gradually increased to 2.75 mA, the average frequency of atonic seizures decreased from six to one per day. The patient became more alert and was able to manipulate the magnet when she had the feeling that a complex partial seizure would begin. The convulsive seizures became rare. Temporary switching to rapid cycle stimulation (on-time: 7 seconds; off-time: 14 seconds) failed to further reduce the seizure frequency. She is currently treated with lamotrigine 250 mg/day, carabamazepine 1200 mg/day and gabapentin 1200 mg/day.

Case 3

A 35 year-old right-handed female with a history of sinusitis, common migraine and a few episodes of severe depression requiring admission presented with a first generalized tonic–clonic seizure at the age of 26 years, a few days after delivering her first and healthy newborn. EEG and computed tomography (CT) were normal and the patient remained untreated. At the age of 28 years she was admitted in a regional hospital because of generalized status epilepticus. Low-field MRI of the brain was negative. She was treated with valproate but continued to have episodes of loss of consciousness and aversive movements of the head and the eyes to the left side, followed by left-sided hemifacial twitching and loss of speech during 60–120 seconds. At the time of the evaluation in our institution, these episodes occurred at least twice a month. There was occasional secondary generalization. In the previous 3 years she had been admitted at least four times for focal motor status epilepticus. The patient was treated with valproate 1000 mg/day and carbamazepine 800 mg/day. Video-EEG monitoring demonstrated left-sided sharp transients, predominantly in the posterior electrode contacts. The ictal semiology suggested a right-sided frontal seizure onset; the ictal EEG showed bilateral recruitment of sharp waves in the parasaggital electrode positions. Optimum MRI showed a large zone of focal cortical dysplasia without specific signal abnormalities in the right-sided prerolandic area. Interictal FDG-PET demonstrated an area of right-sided hypometabolism in the frontal lobe. Neuropsychological evaluation did not reveal specific abnormalities. The patient was felt not to be a suitable candidate for resective epilepsy surgery because of the location and extent of the structural abnormality. She was subsequently offered VNS. The surgical procedure was performed in March 1995 and the perioperative period was uneventful. The stimulation output was gradually increased to 2.5 mA with standard stimulation parameters. Hoarseness during the stimulation trains required decreasing the output to 2.25 mA. Weeks after the implantation the patient became free of generalized convulsions; she also stopped having loss of contact during her episodes. The habitual seizures consisted of twitching of the left hand and dystonic posturing during seconds to minutes with an average frequency of one to two per month. Use of the magnet failed to reduce the frequency of the simple partial seizures. The patient was further treated with a combination of carbamazepine, phenobarbital and clonazepam. She was able to resume her work as a housekeeper and had a second and uneventful pregnancy. She was followed at regular 4–6 month intervals but missed several appointments during the year 2000. In November 2000, the patient was admitted into a regional hospital after she had had a generalized convulsion for the first time in 5 years. A routine check of the NCP^{TM} device showed an end-of-life status of the battery. In the weeks that followed and before a new generator could be implanted because of an administrative delay with

the reimbursement agency, the patient became very depressed. Mid-December 2000, a new NCP^{TM} device was implanted. The stimulation output was rapidly increased to 1.75 mA. The patient was also treated with venlafaxine, a major antidepressant, at a dose of 37.5 mg/day. At the time of her last follow-up visit she was again free of convulsive and complex partial seizures but continued to have focal motor seizures. She was able to resume most of her work in the household. The antiepileptic drug regimen was unchanged. The treatment with venlafaxine had been stopped a few weeks earlier.

Self-assessment questions

Which of the following statements are true?

Question 1. The case:

(a) Despite adequate anti-epileptic treatment, 30% of patients continue to have seizures or experience unacceptable pharmacological side effects.

(b) 50% of patients who undergo resective surgery where the epileptogenic zone can be identified become seizure-free.

(c) Administration of new anti-epileptic drugs in candidates who are unsuitable for resective surgery will lead to seizure freedom in a maximum of 7% of patients.

Question 2. History/anatomical basis:

(a) The first vagus nerve stimulator implanted in humans was in 1990.

(b) The left vagus nerve consists of 80% efferent fibres and about 20% afferent fibres.

(c) Afferent fibres have their origin in the nodose ganglion and primarily project to the nucleus of the solitary tract.

(d) The nucleus of the solitary tract has widespread projections to numerous areas in the forebrain as well as the brain stem including important areas for epileptogenesis such as the amygdala and thalamus.

(e) Heart rate is mostly influenced by the left vagus nerve.

Question 3. Mechanisms of action:

(a) In animal experiments, VNS can induce EEG synchronization, EEG desynchronization, rapid eye movement and sleep or slow-wave sleep.

(b) VNS acts through a release of neurotransmitters and other compounds at the projection site of the vagus nerve.

(c) c-fos studies have shown that key structures in the neuronal network are activated during VNS.

(d) Changes in supratentorial and cerebellar CBF caused by acute and chronic VNS have been demonstrated.

Question 4. VNS and surgical procedure:

(a) VNS involves a surgical procedure where a pulse generator and a bipolar lead are implanted during a 1–2 hour operation.

(b) Once implanted the generator is switched on and stimulation is continuous.

(c) The generator can be programmed using a magnet.

(d) The patient has no control over the generator.

Question 5. Results:

(a) Two randomised, blinded, active control trials (E03 and E05) have been conducted in a total population of 310 with patients with refractory partial epilepsy.

(b) In the EO3 and EO5 trials, in the patients in the high stimulation group there was a mean reduction in seizure frequency of 24% and 28% respectively.

(c) The most common treatment-related adverse events which occur during 'on' periods are voice alteration, coughing, throat paraesthesia and discomfort and dyspnoea.

(d) Bradycardia and asystole are common complications during intraoperative testing.

(e) Patients treated with VNS have a higher rate of sudden unexpected unexplained death (SUDEP) compared to patients treated with novel anti-epileptic drugs.

(f) The SUDEP rate became lower during a 2-year follow-up.

Question 6. Long-term effects and cost-benefit issues:

(a) VNS remains effective over time and there is a trend towards improved seizure control with longer use of VNS.

(b) There are no chronic side effects with VNS.

(c) In a 5-year follow-up, 44% of patients reported a large reduction in seizure frequency and severity.

(d) There is no change in the epilepsy-related direct medical costs after implantation with the vagus nerve stimulator.

(e) The battery life of the generator is estimated to be 8 years.

(f) In a comparative study of conservative treatment, resective epilepsy surgery and VNS, VNS was demonstrated to have favourable cost efficacy in patients who were unsuitable candidates for resective surgery.

Answers

Question 1. The case:

(a) true.

(b) false—60–90% of patients who undergo resective surgery where the epileptogenic zone can be identified become seizure-free.

(c) true.

Question 2. History/anatomical basis:

(a) false—the first vagus nerve stimulator implanted in humans was in 1988.

(b) false—the left vagus nerve consists of about 80% afferent fibres and about 20% efferent fibres.

(c) true.

(d) true.

(e) false—heart rate is mostly influenced by the right vagus nerve.

Question 3. Mechanisms of action:

(a) true—depending on the level of anaesthesia and the stimulus parameters used.

(b) unsure—while there have been studies showing changes in amino-acid and neurotransmitter metabolite concentrations in CSF samples before and after VNS, it remains to be clarified whether these findings are epiphenomena or directly related to VNS.

(c) true.

(d) true.

Question 4. VNS and surgical procedure:

(a) true.

(b) false—stimulation can be initiated immediately after the surgery or after the patient has fully recovered from the surgery, typically 1–2 weeks later.

(c) false—the generator is programmed with a radio frequency telemetry wand connected to an IBM compatible computer.

(d) false—the patient/carer can use the magnet to deliver additional stimulation in case of an aura or seizure or if kept over the generator the magnet will inhibit the stimulation.

Question 5. Results:

(a) true.

(b) true.

(c) true.

(d) false—bradycardia and asystole have been reported as rare complications during intraoperative testing, probably due to stimulation of the cervical cardiac branches of the vagus nerve either directly or by collateral current spread.

(e) false—patients treated with VNS have a comparable rate of sudden unexpected unexplained death compared with patients treated with novel anti-epileptic drugs.

(f) true.

Question 6. Long-term effects and cost-benefit issues:

(a) true.

(b) false—chronic side effects were identical to those observed during the randomized trials.

(c) true.

(d) false—a study showed that there is a significant decrease in epilepsy-related direct medical costs after implantation.

(e) true.

(f) true.